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FORT KNOX, KENTUCKY

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INFLUENCE OF POLYVINYL-PYRROLIDONE COMPOUNDS ON THE POST-IRRADIATION SYNDROMES*

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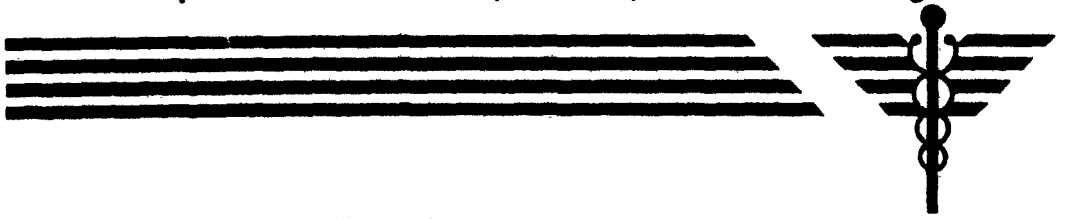

RESEARCH AND DEVELOPMENT DIVISION
OFFICE OF THE SURGEON GENERAL
DEPARTMENT OF THE ARMY

REPORT NO. 229

INFLUENCE OF POLYVINYL-PYRROLIDONE COMPOUNDS ON THE POST-IRRADIATION SYNDROME*

by

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*Subtask under Biological and Medical Aspects of Ionizing Radiation, AMRL Project No. 6-59-08-014, Subtask, Effects of Ionizing Radiation.

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ABSTRACT

INFLUENCE OF POLYVINYL-PYRROLIDONE COMPOUNDS ON THE POST-IRRADIATION SYNDROME

OBJECT

To repeat studies on the use of the polyvinyl-pyrrolidone compounds as possible antidotes for the post-irradiation syndrome and to discuss possible reasons for the discrepancy in reported investigations.

RESULTS AND CONCLUSIONS

Under strictly controlled conditions (critical dose range, relatively soft radiation and proper amount of substance) the low-molecular weight polyvinyl-pyrrolidone compound, Periston "N" exhibited a tendency to influence benefically the post-irradiation syndrome in total body x-irradiated mice. No protection was afforded by the high molecular weight compounds which, instead added to the irradiation stress.

The beneficial effect, afforded by Periston "N" was slight but worthy of consideration. Acting as a possible "wash-out" of radiation produced substances, it appears to support the idea of the use of low molecular weight polyvinyl-pyrrolidone as an antidote in the post-irradiation syndrome.

RECOMMENDATIONS

To evaluate these possibilities, experiments with very soft radiation should be done. Urine from Periston "N" treated animals and from control irradiated animals should be examined for toxic substances.

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INFLUENCE OF POLYVINYL-PYRROLIDONE COMPOUNDS ON THE POST-IRRADIATION SYNDROME

I. INTRODUCTION

Since Jacobson's first publication on the post-irradiation protection afforded by spleen and spleen tissue homogenate, much work has been devoted to the study of post-irradiation protection by biological and physiological means. Systematic studies on the possibility of post-irradiation protection by pharmacological means are not as numerous.

An interesting approach was described in 1953 by Rugh, Suess and Scudder (1). They discussed the use of polyvinyl-pyrrolidone (PVP) as a possible antidote for the post-irradiation syndrome. However, using PVP-macrose and PVP-dextrose, they did not find any protective action of these compounds (average molecular weight about (40,000) on mice exposed to 700 r total body x-irradiation (210 kv with 0.5 mm Al and 0.28 mm Cu filtration). Similar results were reported in 1955 by Upham et al (2), who studied the tissue deposition of PVP (average molecular weight about 40,000) in normal and total body x-irradiated rabbits (500 r/air; 700 r/air; 250 kv, 0.20 mm Cu inherent plus 1 mm Al).

Contrary to these findings Burger, Grabinger and Lehmann (3), using the low-molecular weight PVP-compound Periston "N" (average molecular weight about 12,600), reported beneficial effects of this compound in total body x-irradiated rats (1000 r, 1500 r; 185 kv and no added filtration).

The different findings in these studies could be attributed to a difference in species. They could be explained also by a difference in quality and quantity of the applied radiations as well as by the fact that low molecular-weight PVPs are powerful detoxifying agents, while high molecular weight PVP-compounds, due to their slower excretion via the kidneys, exhibit this effect to a much lesser degree (4).

To evaluate the different factors, systematic studies on the post-irradiation protection afforded by PVP to total body x-irradiated mice were started. Difference in x-ray dose, in x-ray quality, in PVP-molecular weight and in the amounts of PVP administered were investigated. Special emphasis was given to Periston "N", a 6% solution of

kollidon (polyvinyl-pyrrolidone) with an average molecular weight of 12,600 (5)*.

II. EXPERIMENTAL AND METHODS

The experiments were done with female CF-1 mice weighing 21 ± 2 grams. A total of 875 animals was used for a study of the toxicity of the compounds, the influence of molecular weight, radiation quality and radiation dose.

The irradiations were done with a General Electric Maxitron therapy unit. For the softer radiation studies the unit was operated at 100 kv, 30 ma, 50 cm TSD, 4.75 mm Be inherent filtration, no filter added, dose rate in air-170 r/min. The harder radiation was given at 250 kv, 1 mm Al + 0.5 mm Cu added filtration, dose rate in air-115 r/min; all other conditions remained unchanged.

The PVP-compounds were injected intraperitoneally 1, 24, 48 and 72 hours after irradiation. Saline was injected into the controls.

The animals were fed Stock Purina chow pellets and given water ad libitum. They were observed for 30 days and the number of deaths was recorded every 24 hours.

III. RESULTS

A. Toxicity Studies

The toxicity of Periston "N", Plasdone, K-21, K-30, K-60 and K-90 was determined. The substances were injected intraperitoneally in amounts of 0.25, 0.5, 1.0, 2.0 and 3.0 cc per injection. Thus, each of these amounts of each substance was injected 4 times at 24-hour intervals. They were found to be harmless to the animals as measured by 30-day survival observations.

B. Survival Studies

1. Influence of PVP-molecular weight.

Mice irradiated with a relatively soft radiation (100 kv and 700 r/air) responded characteristically to PVP compounds of

*Periston"N" is produced by Farbenfabriken Bayer, Leverkusen, Germany and is recommended for "serum and tissue-lavage". The Periston "N" used in these experiments was generously supplied by Farbenfabriken Bayer, Leverkusen, Germany.

different molecular weights, when administered after irradiation. The animals treated with the low-molecular weight Periston "N" (average molecular weight about 12,600) showed 98% survival after 30 days, while mice treated with PVPs of higher molecular weight showed lower percentage survivals than untreated irradiated animals (Fig. 1). None of the tested PVP-compounds exercised a beneficial effect on mice irradiated with 250 kv x-rays (700 r/air). The survival curves show the same general pattern for all PVPs studied (Fig. 2).

2. Influence of Periston "N" amounts

The amount of Periston "N" administered after irradiation also influenced the results. Injections of 0.5 cc were beneficial to the survival of mice irradiated with 700 r kv (Fig. 3). With increased doses of radiation none of the Periston "N" amounts were beneficial. Increased amounts seemed to add to the stress and accelerated post-irradiation death. This is in accordance with similar findings by Rugh et al (Fig. 4 and 5).

IV. DISCUSSION

The idea of using PVP as a possible antidote for the post-irradiation syndrome is based on 2 facts; the existence of a toxic substance produced by irradiation (6)-"radiogenic toxins" according to Rugh et al (1) and the observations that PVP, a powerful anti-shock agent exercises strong in vivo detoxifying action against certain toxins, including diptheria, botulinus and tetanus toxins (4, 5 and 7). If this anti-toxic action of PVP were efficacious in general--such was the original reasoning (1 and 3)--then PVP also could be expected to be beneficial in the toxemia and shock following acute x-irradiation exposure.

The experiments of Rugh et al and the findings of Upham and co-workers do not confirm this speculation. On the contrary, the administration of PVP-macrose and PVP-dextrose (average molecular weight about 40,000) to irradiated mice added to the stress and accelerated post-irradiation death. Thus, the assumption on which the use of PVP in the post-irradiation syndrome was based, appeared invalid--if it were not for the positive results reported by Burger and his group. These experiments were done with the especially low-molecular weight PVP Periston "N" (average molecular weight about 12,600) and they call attention to an undiscussed factor--the role of the molecular weight of PVP in its detoxifying action. Clinical as well as experimental

studies give evidence that PVP acts as a detoxifying agent by absorbing the toxins and excreting them through the kidneys. Since low-molecular weight PVPs can pass the kidney barrier easier and faster than PVPs with average molecular weights of 40,000 and higher (4, 5, 7 and 8), it could be assumed that the original concepts (toxic substance produced by radiation; non-specific, detoxifying action of PVP) may still hold and that the results of Rugh et al and of Upham and co-workers were caused by the fact that high-molecular weight PVPs were used in their experiments.

The results of the present study support this conclusion. High molecular weight PVPs did not exercise protective action after irradiation, regardless of the conditions of the experiment (dose, radiation quality and amount of PVP administered). Low-molecular weight PVPs such as Periston "N" showed a tendency toward protective action (Fig. 1). The beneficial effect was quite small. It appeared to be confined to a certain dose range (not 100% lethal), relatively soft radiation, and dependent upon the amount of PVP administered. This may be attributed to the fact, mentioned by Rugh et al, that toxemia and shock from acute irradiation exposure differ from toxemias and shock brought about by trauma, hemorrhage and burns. Thus PVP, efficacious in toxemia, trauma, hemorrhage and burn damage, may be only partially efficacious for radiation-toxemia and radiation-shock.

The dependence upon radiation quality might be explained by the higher absorption coefficient of skin for softer radiation, in connection with the fact that Periston "N" is deposited mostly in the skin (9). Also, it could be speculated that harder radiations, hitting more and different organs, may produce tissue specific toxic substances (10) which behave differently toward the detoxifying action of Periston "N"; a problem connected with midline dose considerations.

V. CONCLUSIONS

Systematic studies of the influence of different PVP-compounds on the post-irradiation survival of total body x-irradiated mice confirm in principle the original idea of using the anti-shock and detoxifying action of such compounds in counteracting the post-irradiation syndrome.

Under strictly controlled conditions (critical dose range, relatively soft radiation, and limited amounts of the PVP) low molecular weight PVPs, such as Periston "N" exhibit a tendency to influence beneficially

the post-irradiation syndrome. The beneficial effect is small; established, however, in repeated experiments, it appears to support the idea on a possible "wash-out" of radiation produced toxins.

VI. RECOMMENDATIONS

The excretions (urines) of Periston "N"-treated and non-Periston "N"-treated irradiated animals should be checked systematically for toxic effects on biological objects using proper controls (11).

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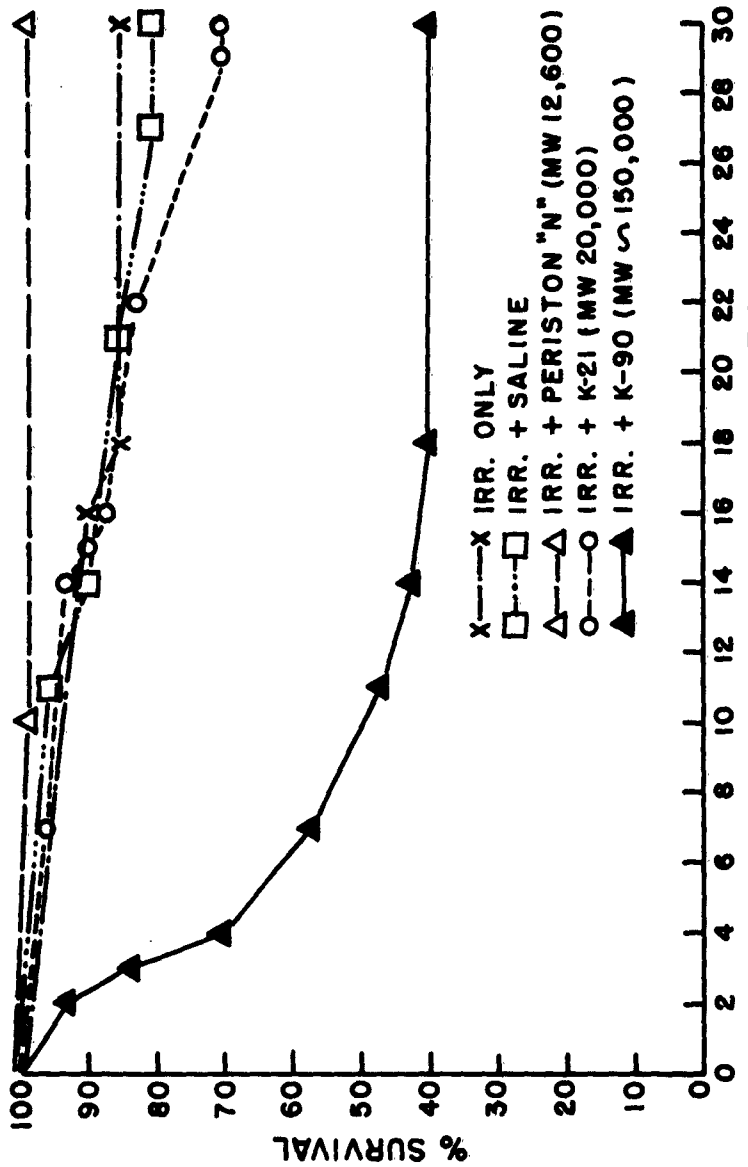

FIG. I INFLUENCE OF PVP MOLECULAR WEIGHT ON IRRADIATION SURVIVAL, 100 KV-X-RAYS, 700 r, FOUR 0.5cc INJECTIONS 24 HOURS APART.

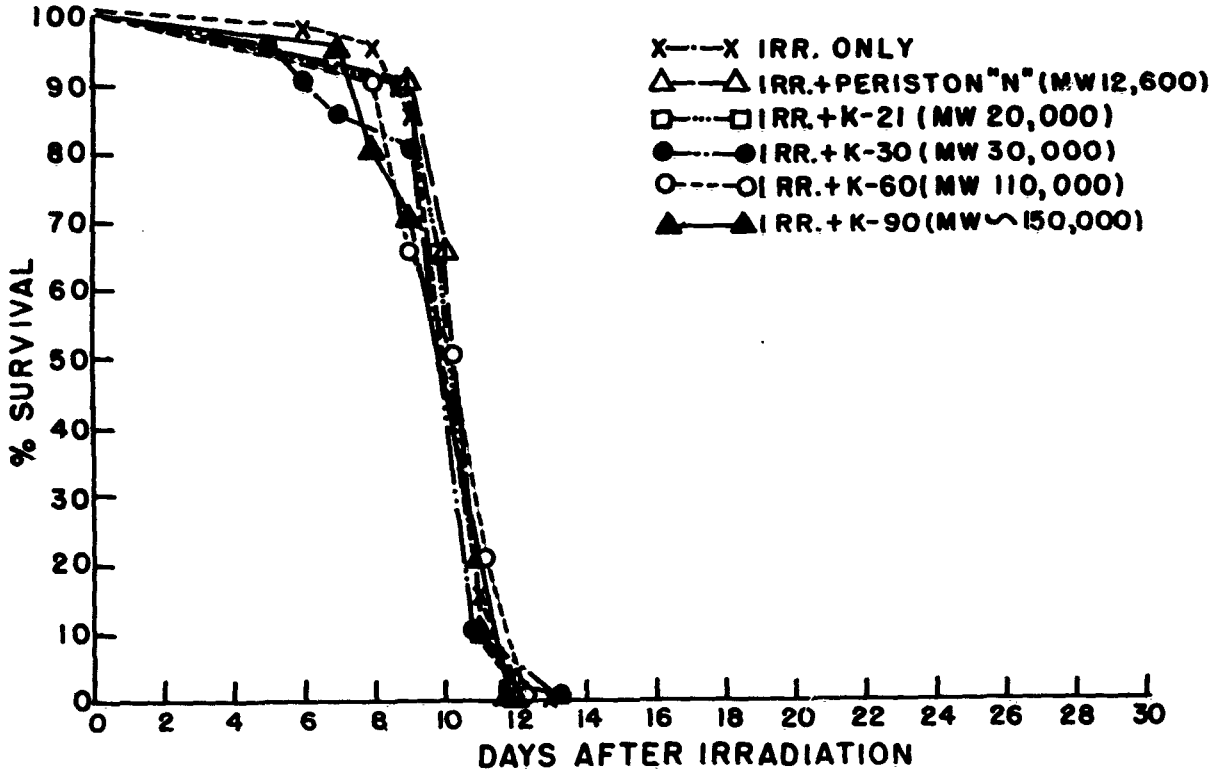

FIG. 2 INFLUENCE OF PVP MOLECULAR WEIGHT ON IRRADIATION SURVIVAL, 250 KV-X-RAYS, 700r, FOUR 0.5cc INJECTIONS 24 HOURS APART.

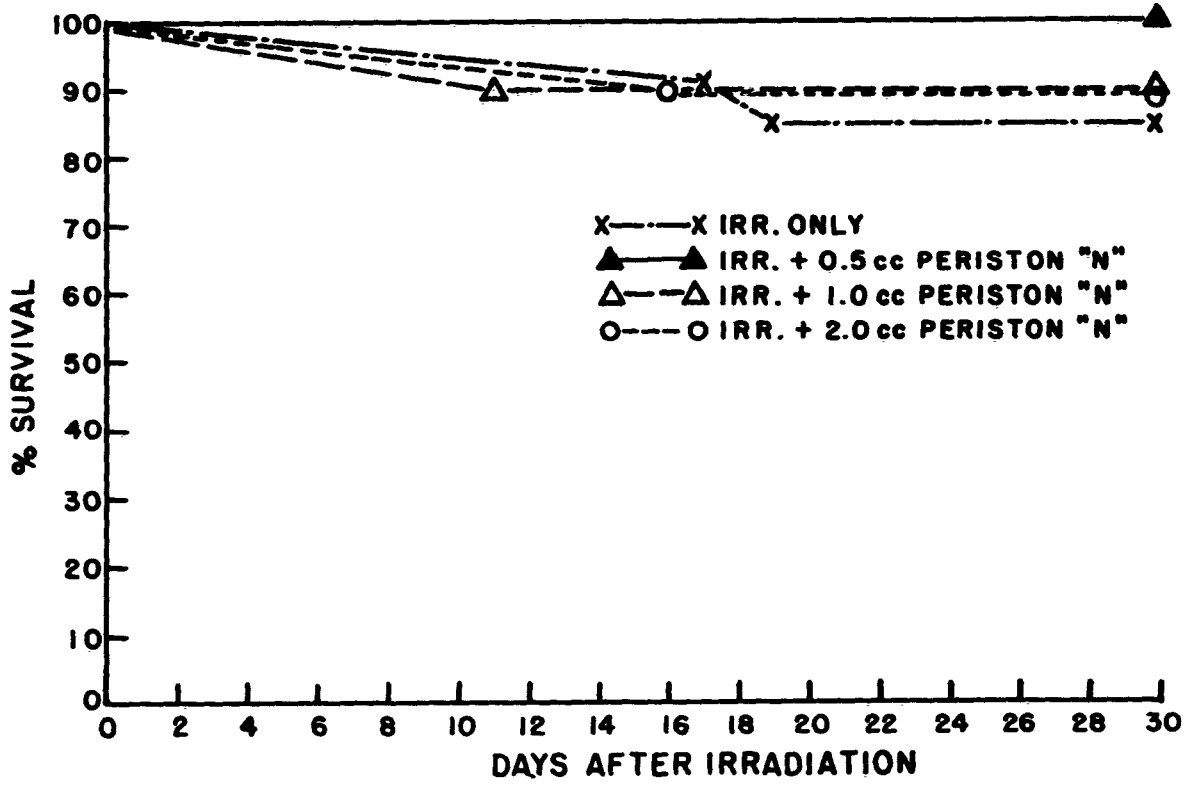

FIG. 3 INFLUENCE OF PERISTON"N" AMOUNTS ON IRRADIATION SURVIVAL, 100 KV-X-RAYS, 700r, FOUR INJECTIONS 24 HOURS APART.

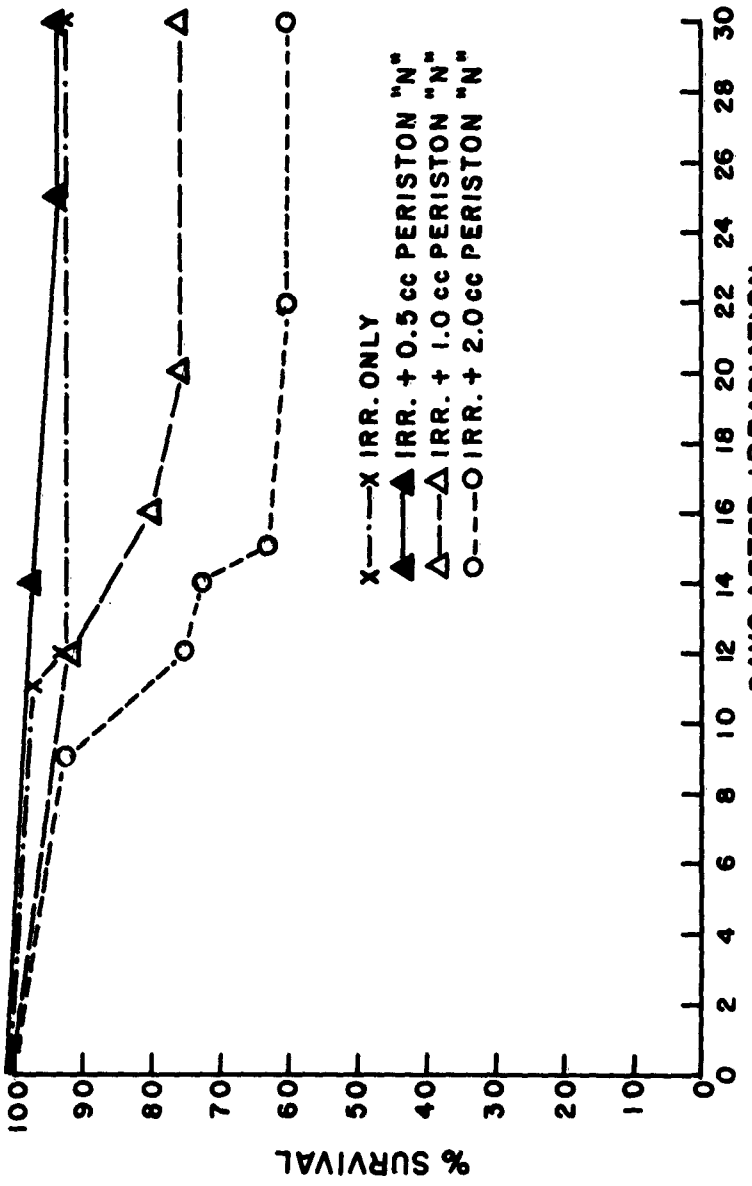

FIG. 4 INFLUENCE OF PERISTON "N" AMOUNTS ON IRRADIATION SURVIVAL, 100 KV-X-RAYS, 900 r, FOUR INJECTIONS 24 HOURS APART.

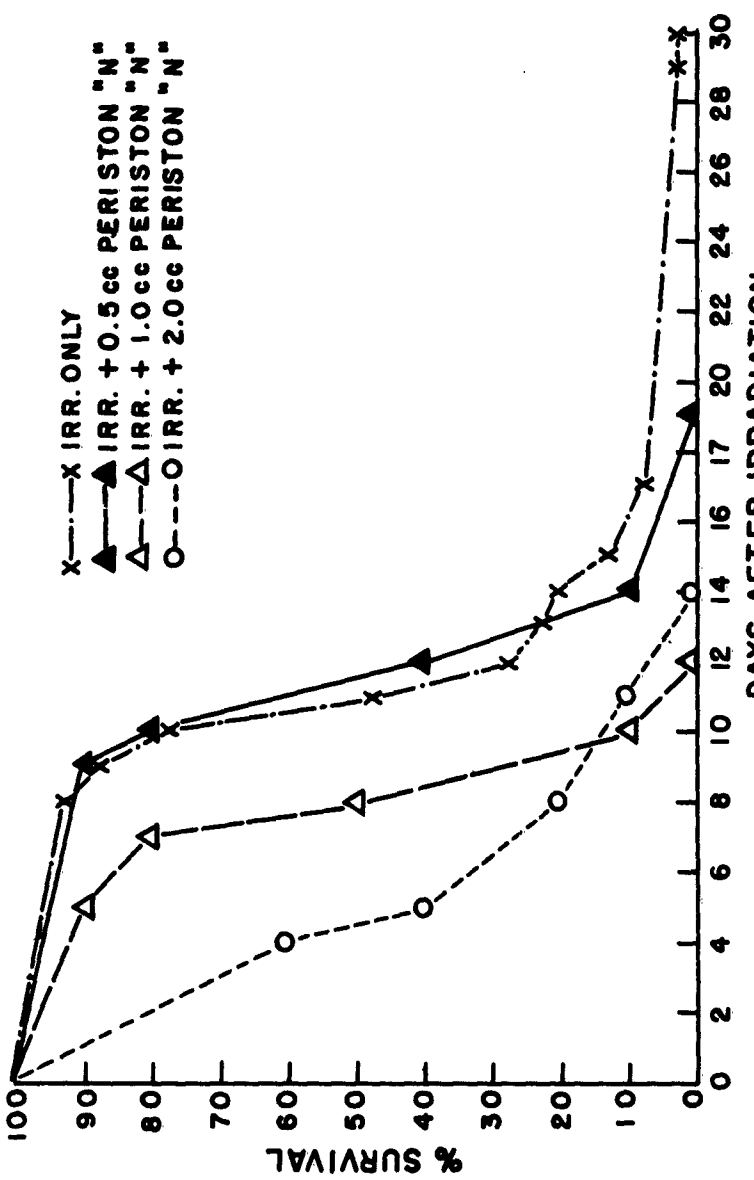

FIG. 5 INFLUENCE OF PERISTON "N" AMOUNTS ON IRRADIATION SURVIVAL, 100 KV-X-RAYS, 1100 r, FOUR INJECTIONS 24 HOURS APART.

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